

Rigidoporus corticola Colonization and Invasive Fungal Disease in Immunocompromised Patients, United States

Alvaro C. Laga, Jessica W. Crothers, Connie F. Cañete-Gibas, Nathan P. Wiederhold, Isaac H. Solomon

We report 2 cases of *Rigidoporus corticola* (*Oxyporus corticola*) infection in humans in the United States. Clinical manifestations consisted of angioinvasive fungal sinusitis in 1 patient and pulmonary intracavitary fungus ball in the other patient. These cases illustrate previously undescribed clinicopathologic manifestations of infection by this filamentous basidiomycete in humans.

Rigidoporus corticola is a white-rot decay fungus of plants and is widely distributed in North America and Europe (1). *R. corticola* is a filamentous basidiomycete in the *Agaricomycotina* subphylum, also known as *Oxyporus corticola* because no morphologic differences or type species are in the same phylogenetic clade. *Rigidoporus* is the preferred name because it was described prior to *Oxyporus* (2,3).

Filamentous basidiomycetes occur in the environment as gilled mushrooms and shelf or bracket fungi (4). Filamentous basidiomycetes (other than *R. corticola*) have been documented in immunocompetent and immunocompromised persons (5,6), but *R. corticola* has not been established as an agent of human disease. We describe the clinical, microbiologic, and histopathologic features of 2 cases of human *R. corticola* infection in the United States (Table).

The Study

The first patient was a 43-year-old man with chronic granulomatous disease and recurrent acute myeloid leukemia in whom hemifacial pain developed after

he received induction chemotherapy. Magnetic resonance imaging showed mucosal thickening and opacification of the patient's left sinuses (Figure 1, panel A). Nasal endoscopy revealed a black eschar on the middle turbinate, which our clinical colleagues interpreted as highly characteristic of mucormycosis, and we performed surgical debridement. Histologic sections showed numerous thin hyaline septate hyphae ($\approx 5 \mu\text{m}$ in diameter) with predominantly 90° -angle branching but no conidiogenous cells or conidia (Figure 1, panel B). We noted vascular invasion and infiltrative growth into sinonasal ossicles (Figure 1, panels C, D). Careful examination revealed bulge and hook-like hyphal outgrowths compatible with clamp connections (Figure 1, panels E, F), which are characteristic of filamentous basidiomycetes. Concurrent fungal culture on Sabouraud dextrose agar grew white cottony colonies. Lactophenol cotton blue preparation from subcultures onto potato flake agar revealed thin sterile hyphae. We sent a culture to the Fungus Testing Laboratory (FTL) at the University of Texas Health Science Center (San Antonio, Texas, USA). FTL also noted growth on benomyl agar suggesting a possible basidiomycete. FTL amplified genomic DNA from the isolate and sequenced for the internal transcribed spacer (ITS) and large subregion (D1/D2) of the 28S rRNA gene (BMBC-R/NL4). Compared with sequences from the NCBI database (<https://www.ncbi.nlm.nih.gov>), most blastn matches were *R. corticola*, 98.53%–100% similarity for ITS and 98.55%–100% for D1/D2; subsequent phylogenetic analysis confirmed *R. corticola* (Appendix, <https://wwwnc.cdc.gov/EID/article/28/4/21-1987-App1.pdf>). Antifungal susceptibility testing demonstrated similar MIC values for voriconazole (0.5 $\mu\text{g}/\text{mL}$) and isavuconazole (1 $\mu\text{g}/\text{mL}$) but a high MIC (8 $\mu\text{g}/\text{mL}$) for posaconazole. The patient was initially treated empirically with liposomal amphotericin B for 20

Author affiliations: Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts, USA (A.C. Laga, I.H. Solomon); University of Vermont Medical Center, Burlington, Vermont, USA (J.W. Crothers); University of Texas Health San Antonio, San Antonio, Texas, USA (C.F. Cañete-Gibas, N.P. Wiederhold)

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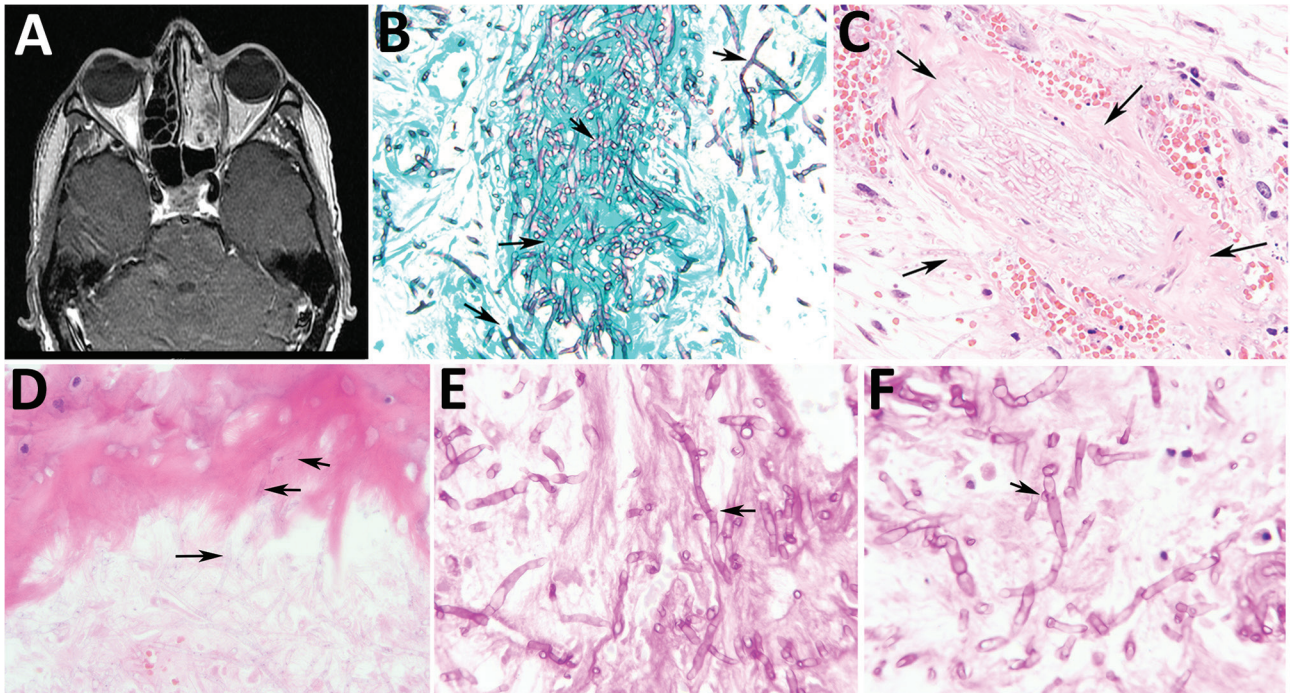


Figure 1. Radiologic and pathologic findings in a 43-year-old immunocompromised man with chronic granulomatous disease and diagnosed invasive fungal sinusitis caused by *Rigidoporus corticola* (*Oxyporus corticola*) infection, United States. A) Magnetic resonance imaging of the head showing mucosal thickening and near opacification in the left frontal, left ethmoid, left maxillary, and left sphenoid sinuses, and the left nasal cavity. No findings suggest extra-sinus extension. B) Debrided sinus tissue stained with Gomori methenamine silver. Arrows indicate numerous septate hyphae with predominantly right-angle branching. Original magnification $\times 600$. C) Hematoxylin and eosin stain of blood vessels. Arrows indicate permeation (angioinvasion). Original magnification $\times 600$. D) Hematoxylin and eosin stain of the sinonasal ossicles. Arrows indicate infiltration consistent with invasive fungal disease. Original magnification $\times 600$. E, F) Periodic acid-Schiff-diastrase-stained sinus tissue. Arrows indicate bulge-like (E) and hook-like (F) hyphal outgrowths potentially representing clamp connections characteristic of filamentous basidiomycetes, that were detected upon careful examination. Original magnification $\times 1,000$.

days, then was transitioned to voriconazole after fungal identification and susceptibility testing. However, the patient experienced recurrent episodes of neutropenic fever and died 10 months later of invasive fungal disease. We presumed the infection to be aspergillosis on the basis of increased serum galactomannan on sequential samples, but this assumption was not confirmed by culture or PCR.

The second patient was a 63-year-old man with a history of lung adenocarcinoma and a new 2.4 cm right upper lobe mass resected for possible recurrence (Figure 2, panel A). Histologic sections showed a cavitory lesion with necrotic center and peripheral fibrous capsule (Figure 2, panel B). Sections stained with Gomori methenamine silver showed numerous septate hyphae in the cavity but no invasion into blood vessels or surrounding tissue (Figures 2, panels C, D). Neither conidiogenous cells nor conidia were evident; we did not identify clamp connections in samples after careful examination. The Centers for Disease Control and Prevention (Atlanta, Georgia, USA) identified *O. corticola* (*R. corticola*) by PCR from

formalin-fixed, paraffin-embedded (FFPE) tissue sections of the wedge resection. We did not attempt culture, and the patient did not receive antifungal therapy. He died 11 months later of recurrent lung adenocarcinoma.

Conclusions

Filamentous basidiomycetes are common environmental fungi increasingly recognized as agents of human disease, causing saprobic colonization of the respiratory tract, allergic disease, and invasive fungal infections (6,7). A review of 218 pathogenic cases reported worldwide found the most common species are *Schizophyllum commune* (52%), *Hormographiella aspergillata* (5.9%), and *Ceriporia lacerata* (5%) (7). Anecdotal reports describe galactomannan and β -d glucan production by filamentous basidiomycetes such as *H. aspergillata*, suggesting that testing for these polysaccharides might help diagnose invasive disease.

Two cases of *R. corticola* infection have been reported in canines. One was a disseminated *R. corticola* infection reported in 2009 in a German shepherd dog,

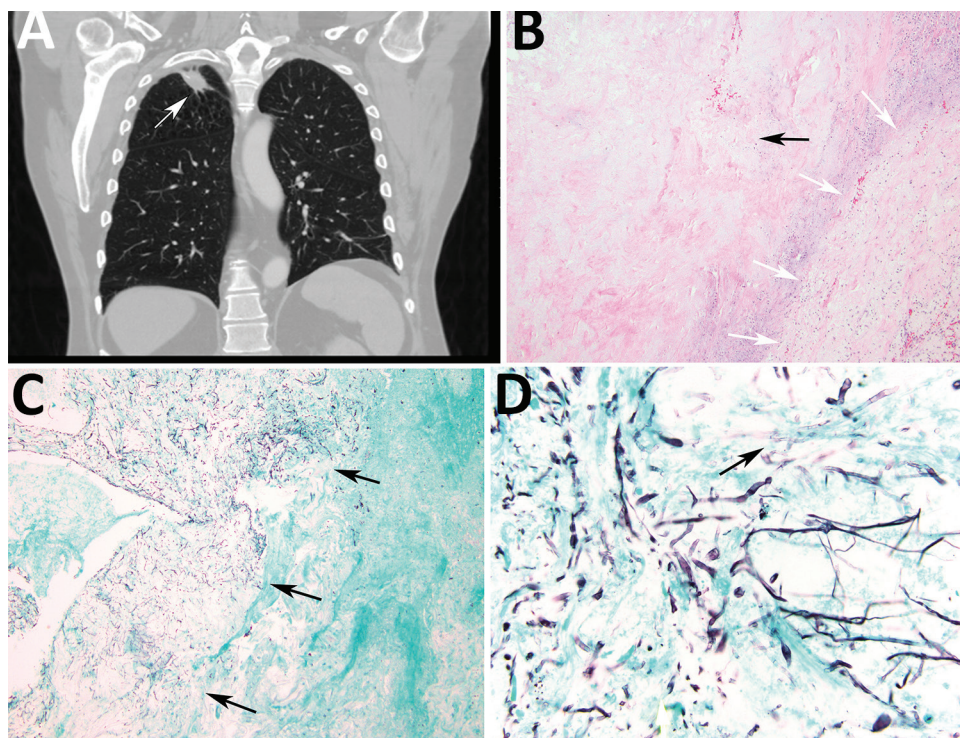
which was ultimately euthanized 20 months after clinical presentation because of progressive disease and central nervous system involvement despite therapy with itraconazole and terbinafine (1). Another case, in 2012, was reported as generalized lymphadenopathy in a beagle, which was confirmed by sequencing of a culture isolate to be caused by *R. corticola* (8). This dog also was euthanized because of progressive disease despite empiric treatment with itraconazole 14 weeks after clinical presentation (8). Histopathology from both canine cases showed septate branching hyphae with parallel to slightly tapering walls.

We document *R. corticola* as an agent of human disease in 2 immunocompromised patients; the fungus colonized the pulmonary cavity of one patient and caused invasive sinusitis in the other. The spectrum of disease we describe resembles that observed for other filamentous basidiomycete fungi. Our findings align with the literature; these organisms are difficult to identify by *in vitro* culture because of lack of sporulation and are not yet reliably identifiable by mass spectrometry (9). Standard sequencing of 18S, 28S, or ITS rRNA and other fungal genomic regions can assist in species-level identification, but accurate identification is limited by available sequencing databases (10–12). However, molecular identification of

fungi by itself is insufficient to establish pathogenicity because it might not distinguish between an agent of disease and a contaminant, particularly in cases involving common environmental fungi and uncommon species not established as agents of human disease, such as *R. corticola*. The 2 clinical cases we describe were detected by histopathology, confirming a pathogenic role in invasive fungal disease in 1 case and colonization of an existing cavity in the other, according to current guidelines (13); fungal sequencing of a culture isolate and FFPE tissue subsequently confirmed identification. These data support observations that filamentous basidiomycetes are being recognized more frequently in clinical specimens and that identification by fungal cultures and biochemical methods remains challenging. Consequently, filamentous basidiomycetes and their burden of disease likely are underrecognized.

Although we performed susceptibility testing against 1 isolate according to the Clinical and Laboratory Standards Institute M38 reference standard (10), no breakpoints for antifungal agents against this species have been established. Of note, the MIC for posaconazole was elevated compared with other basidiomycetes reported to cause human infections, such as *S. commune*. Although data are limited,

Figure 2. Radiologic and pathologic findings in a 61-year-old immunocompromised man with a history of lung adenocarcinoma and a new 2.4 cm right upper lobe mass determined to be a pulmonary fungus ball caused by *Rigidoporus corticola* (*Oxyporus corticola*) infection, United States. A) Chest computed tomography scan. Arrow indicates a 2.4 × 2.2 cm ovoid pulmonary mass in the right upper lobe. B) Hematoxylin and eosin–stained histologic sections of the resected mass. Black arrow indicates a cavitory lesion with a necrotic center. White arrows indicate peripheral fibrous capsule. Original magnification ×100. C, D) Gomori methenamine silver–stained histologic sections. C) Arrows indicate numerous hyphae within the cavity, but no evident invasion into blood vessels or surrounding tissue. Original magnification ×40. D) Arrow indicates septate thin hyphae evident in the center of the cavity. Original magnification ×600.



of 5 *R. corticola* isolates in the FTL database with MIC results for posaconazole, 4 had elevated posaconazole MICs (range 2.0 to >16 µg/mL), but voriconazole MICs were lower (range 0.25–1.0 µg/mL). Lack of evidence-based treatment guidelines might have contributed to illness in these patients, both of whom died from complications of their underlying diseases <1 year after seeking care for *R. corticola* infection.

Although filamentous fungi cannot be speciated by histology, detection of the characteristic clamp connections should prompt consideration of filamentous basidiomycetes in the differential diagnosis. Admittedly, this finding might be rare because most clinical isolates are reportedly monokaryons (14), but 1 study documented clamp connections in 78% of clinical isolates of *S. commune* and *C. lacerata* (15).

In summary, our report adds *R. corticola* to the list of increasingly recognized filamentous basidiomycete fungi associated with human disease. Clinicians should consider *R. corticola* when assessing immunocompromised patients for invasive fungal infections or respiratory tract colonization.

About the Author

Dr. Laga is an infectious disease pathology consultant at Brigham and Women's Hospital in Boston, Massachusetts, USA. His primary research interests include medical mycology and tropical and neglected infectious diseases.

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Address for correspondence: Alvaro C. Laga, Brigham and Women's Hospital, Department of Pathology Amory-3, 75 Francis St, Boston, MA 02115, USA; email: alagacanales@bwh.harvard.edu

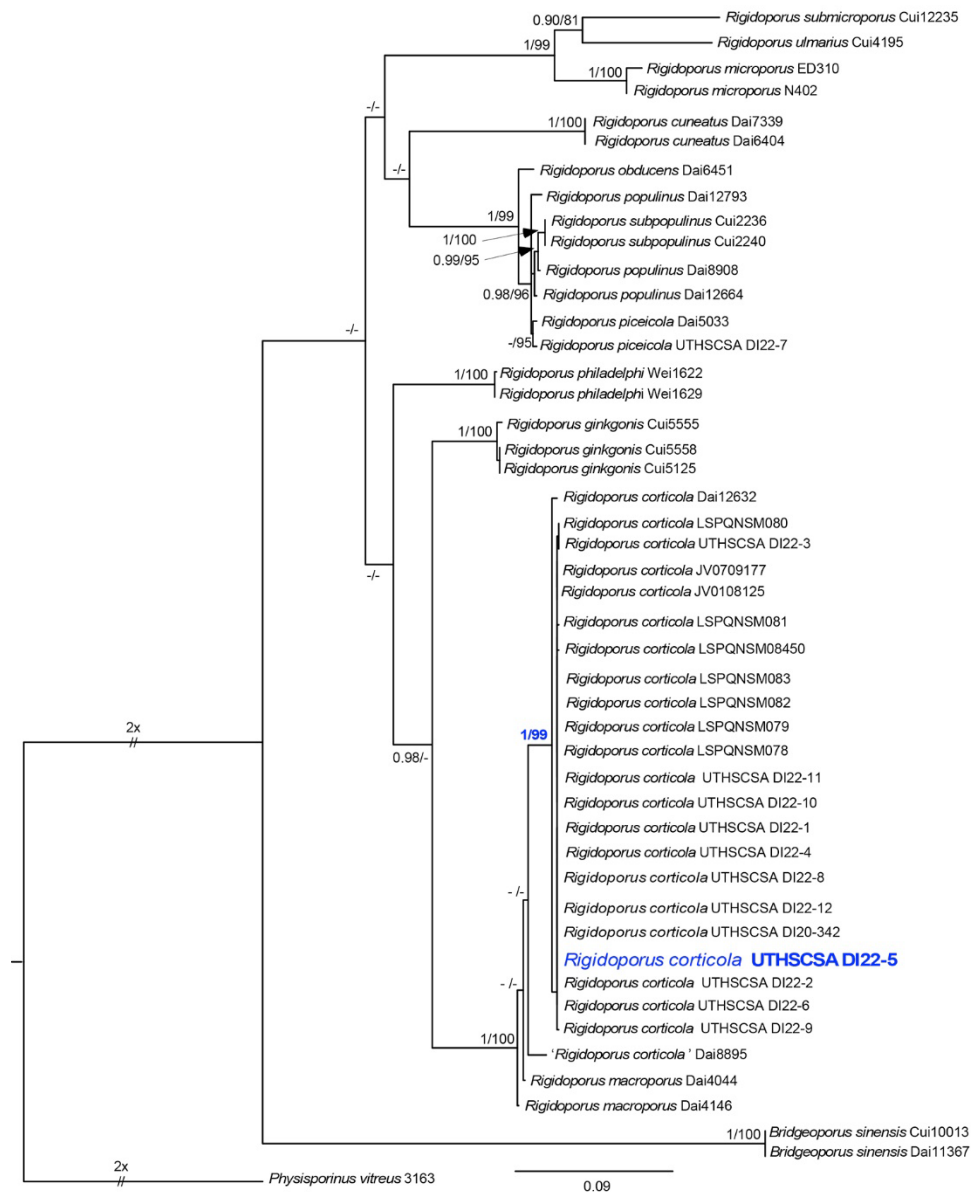
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Appendix

Appendix Table. GenBank accession numbers of internal transcribed spacer (ITS) and large subunit (LSU) sequences of representative taxa listed in Wu et al. reference, and *Rigidoporus corticola* sequences generated from the collection of the Fungus Testing Laboratory (FTL) at the University of Texas Health San Antonio, Texas, USA*

FTL accession no.	ITS GenBank accession no.	LSU GenBank accession no.
UTHSCSA DI22-1	OM127879	OM128160
UTHSCSA DI22-2	OM127880	OM128161
UTHSCSA DI22-3	OM127881	OM128162
UTHSCSA DI22-4	OM127882	OM128163
UTHSCSA DI22-5	OM127883	OM128164
UTHSCSA DI22-6	OM127884	OM128165
UTHSCSA DI22-8	OM127885	OM128166
UTHSCSA DI22-9	OM127886	OM128167
UTHSCSA DI22-10	OM127887	OM128168
UTHSCSA DI22-11	OM127888	OM128169
UTHSCSA DI22-12	OM127889	OM128169
UTHSCSA DI20-342	MW476707	MW478302

*(1) Wu et al. 2017. Bold text indicates case 1 isolate.



Appendix Figure. Phylogenetic tree of internal transcribed spacer (ITS) and large subunit (LSU) sequences of representative taxa listed in Wu et al. (1), and *Rigidoporus coricola* sequences generated from the collection of the Fungus Testing Laboratory (FTL) at the University of Texas Health San Antonio, Texas, USA. The tree shows a subset of the backbone for *Rigidoporus* and related genera and the relationship of isolate UTHSCSA DI22–5 (blue text) from case-patient 1 with other FTL isolates and representative species of *Rigidoporus*. The tree was inferred from combined ITS and partial LSU (D1/D2) sequences by using maximum likelihood general time-reversible plus gamma distribution plus invariable site substitution model in IQ-TREE version 2.1.3 (<http://www.iqtree.org>). Bayesian posterior probabilities were calculated by using MrBayes version 3.2 (<http://nbisweden.github.io/MrBayes>); values ≥ 0.95 and bootstrap values $\geq 80\%$ are shown at the nodes. Scale bar indicated nucleotide substitutions per site. UTHSCSA DI, University of Texas Health at San Antonio deidentified number.

Reference

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